Cascade Reaction of 6-Deoxy-6-iodohexopyranosides Promoted by Samarium Diiodide: A New Ring Contraction of Carbohydrate Derivatives†

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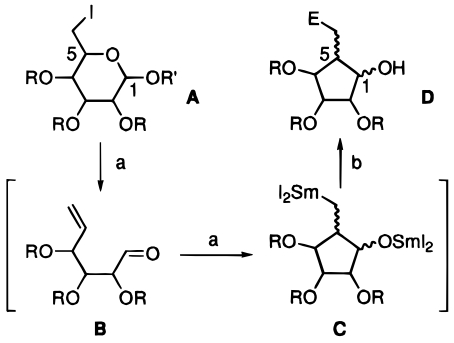
Sequential transformations[1] allow the assembly of complex molecules in a simple manner, with a minimum of purification steps, and are accordingly ideal components of elegant and efficient synthetic strategies. In recent years, samarium diiodide[2] has evolved as a unique single electron reducing agent that is especially well suited to promote sequential processes that combine radical and anionic steps with a high degree of chemo- and stereoselectivity.[3] On the basis of the rich chemistry uncovered for this reagent, we hypothesized that its interaction with a 6-deoxy-6-iodohexopyranoside derivative **A** (Scheme 1) could trigger a reaction cascade that would eventually lead to a novel ring contraction[4,5] of the pyranose moiety. This sequence requires four SET steps (i.e., 4 mol equiv of SmI_2) and consists of (1) a reductive dealkoxyhalogenation to give the ring-opened hex-5-enal **B**;[6] (2) an intramolecular ketyl-olefin reductive coupling affording the ring-contracted organosamarium intermediate **C**,[3a−c,7] and (3) the intermolecular trapping of this organosamarium with appropriate electrophiles to produce finally the branched cyclopentitol derivative **D**.[3a−c]

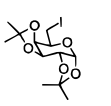
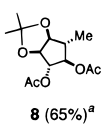
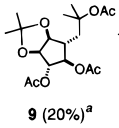
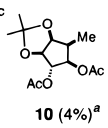
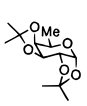
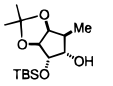
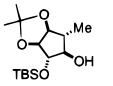
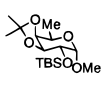
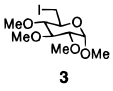
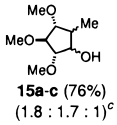
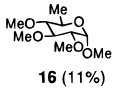
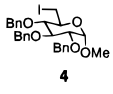
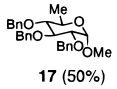
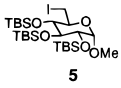
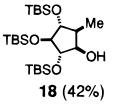
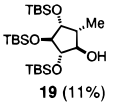
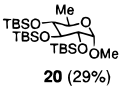
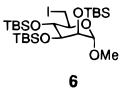
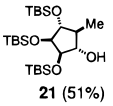
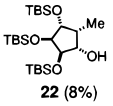
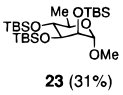
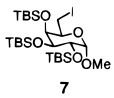
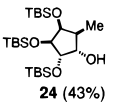
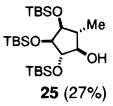
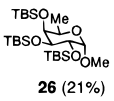
We report here the successful implementation of the postulated process for a series of 6-deoxy-6-iodohexopyranosides (**1**−**7**)[8,9] (Table 1) of different configuration and substitution pattern and initial studies of the influence of the reaction conditions and protecting groups on the outcome of the reaction.

Scheme 1[a]



[a] Reagents: (a) 2 SmI_2; (b) (i) E^+; (ii) H^+.

Table 1. Reaction of 6-Deoxy-6-iodohexopyranosides with SmI_2 in THF−HMPA

Entry	Substrate	Products (isolated yield)			
1	 **1**	 **8** (65%)[a]	 **9** (20%)[a]	 **10** (4%)[a]	 **11** (9%)
2	 **2**	 **12** (47%)	 **13** (17%)[b]	 **14** (11%)	
3	 **3**	 **15a-c** (76%) (1.8 : 1.7 : 1)[c]		 **16** (11%)	
4	 **4**	—		 **17** (50%)	
5	 **5**	 **18** (42%)	 **19** (11%)	 **20** (29%)	
6	 **6**	 **21** (51%)	 **22** (8%)	 **23** (31%)	
7	 **7**	 **24** (43%)	 **25** (27%)	 **26** (21%)	

[a] Products obtained after acetylation of the crude reaction mixture. [b] The stereochemistry of **13** was further confirmed by its transformation into **8** by desilylation (TBAF in THF) followed by in situ acetylation (Ac_2O, pyridine). [c] Inseparable mixture. Ratio determined by ^1H NMR.

Preliminary experiments were performed with compound **1** to determine the optimum reaction conditions. In a typical procedure, a 0.05 M solution of **1** in THF was

† A preliminary report of this work was presented at the XVIIth International Carbohydrate Symposium, Ottawa, July 1994; Abstract B1.67.

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(1) For excellent accounts on the subject, see the recent *Chem. Rev.* thematic issue on "Frontiers in Organic Chemistry": *Chem. Rev.* **1996**, *96* (1).

(2) For a recent review, see: Molander, G. A. *Chem. Rev.* **1996**, *96*, 307−338.

(3) (a) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059−4071. (b) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872−882 and references cited therein. (d) Enholm, E. J.; Jiang, S.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061−4069 and references cited therein. (e) Curran, D. P.; Wolin, R. L. Wolin, R. L. *Synlett* **1991**, 317−318. (f) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773−774.

(4) For a recent highlight on ring contractions in carbohydrates, see: Redlich, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1345−1347.

(5) For a related ring contraction of carbohydrate derivatives using SmI_2, see: Chénedé, A.; Pothier, P.; Sollogoub, M.; Fairbanks, A. J.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1373−1374.

(6) Originally described with Zn or butyllithium by: (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990−2016. For modified procedures, see: (b) Fürstner, A.; Baumgartner, J.; Jumbam, D. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 131−138 and references cited therein. For previous reports on ring scissions of cyclic β-halo ethers promoted by samarium diiodide, see: (c) Crombie, L.; Rainbow, L. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 673−687. (d) *Tetrahedron Lett.* **1988**, *29*, 6517−6520.

(7) (a) Fevig, T. L.; Elliot, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064−5067. (b) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063−1066. (c) Baldwin, J. E.; Turner, S. C. M.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9411−9424.

(8) All new compounds showed correct microanalytical and spectroscopic data.

(9) Compounds **1**−**4** were prepared in high yield by iodination of the corresponding partially *O*-protected pyranosides with the triphenylphospine/imidazole/iodine reagent.[10] Compounds **5**−**7** were prepared in high yield by silylation of the corresponding methyl 6-deoxy-6-iodopyranosides[11] with TBDMSOTf in 2,6-lutidine/CH_2Cl_2.

(10) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866−2869.

(11) Whistler, R. L.; Anisuzzaman, A. K. M. *Methods Carbohydr. Chem.* **1980**, *8*, 227−231.

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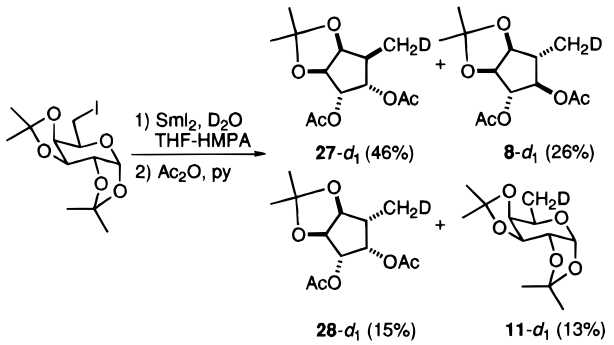
added dropwise to a 0.1 M solution of SmI_2 (6 mol equiv) in THF and HMPA (30 mol equiv) at 22 °C, and the mixture was stirred for 1.5 h. In the case of **1**, the reaction products were better isolated after in situ acetylation of the crude reaction mixture (Ac_2O/pyridine). Three cyclopentane products (**8**−**10**)[8,12] were isolated together with the corresponding 6-deoxypyranoside (**11**). Cyclopentane **9**, which was shown to have the same stereochemistry at the two new stereocenters as the major cyclopentane **8**,[12] probably derives from attack of the major diastereoisomeric organosamarium intermediate **C** on the acetone molecule released from **1** in the reductive elimination step. Lower temperatures favored formation of **11** (12% at 0 °C; 15% at −25 °C; 63% at −78 °C)[13] and produced a decrease in the yield of **9** (3% at 0 °C; 0% at −25 °C or below) without having a significant influence on the diastereoselectivity of the ring-closure reaction. Also important is the influence of the nature of the protecting groups both on the diastereoselectivity (cf. Table 1, entries 1 and 2 and 3 and 5) and on the extent of the competing simple dehalogenation reaction. The highest diastereoselectivity was observed for the transformation of substrate **1** and is probably the result of electrostatic repulsion in the intermediate ketyl radical anion derived from **B**, where O-2 is presumably in the form of a samarium(III) alkoxide. Increasing steric bulk around the halogenated carbon produced an increase in the amount of the simple dehalogenation reaction giving the 6-deoxypyranoside (cf. Table 1, entries 1 and 7 and 3 and 5).[14] Interestingly, in the case of the benzylated derivative **4** the only isolable product was the corresponding 6-deoxypyranoside **17** (Table 1, entry 4).[15] A higher yield of **17** (70%) was obtained when this reaction was performed in the presence of MeOH (30 equiv). In most cases, the cyclic products have the methyl group trans to the hydroxyl group, as expected for these exo cyclizations.[3] In addition, a trans orientation between the hydroxyl and the vicinal alkoxy group at C-2 has been observed in all cases, except in the cyclizations of the silylated galacto derivatives **2** and **7**.[16]

Further efforts were directed at determining some mechanistic aspects of this reaction cascade. Thus, compound **1** was subjected to the standard reaction conditions but 10 equiv of D_2O was added to the SmI_2 solution just prior to the addition of **1**. To our surprise, under these conditions two new cyclopentanes (**27** and **28**)[17] were obtained together with **8** (which was no longer the major product) and the dehalogenated product **11** (Scheme 2), all showing deuterium incorporation at the methyl group as determined by ^1H and ^{13}C NMR.[18] The change in diastereoselectivity induced by the proton source is unprecedented and could be the result of protonation of the O-2 samarium(III) alkoxide in the ketyl radical anion intermediate derived from **B**. Chelation of samarium(III) or intramolecular hydrogen bonding in this radical anion intermediate may account for the predominant formation of **27**.[3c,19,20] The presence of deuterium in the final products indicates the intermediacy of alkyl anions both in the reductive elimination reaction and in the carbocyclization reaction.[6c,3b] In contrast, when the proton source was added immediately after complete consumption of the starting material no deuterium incorporation took place.[3a]

Scheme 2



In conclusion, the process described in this paper represents a new and simple method for the one-pot preparation of highly functionalized, enantiomerically pure cyclopentanes from readily accessible carbohydrate derivatives.[21] Further efforts directed to the trapping of the final organosamarium intermediate with different electrofiles are in progress.

Acknowledgment. Financial support by DGICYT (Grant No. PB93-0127-C02-01) is gratefully acknowledged.

Supporting Information Available: General experimental procedure for the reaction of 6-deoxy-6-iodohexopyranosides with SmI_2, ^1H and ^{13}C NMR data, and 2D NOESY cross-peak intensities for cyclopentane products (4 pages).

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(12) The stereochemistry of the two new centers was determined by ^1H NMR and 2D NOESY studies (see the supporting information).

(13) A similar effect of temperature on the extent of competing dehalogenation vs dealkoxyhalogenation has been previously observed in the reaction of halo sugars with metal−graphite reagents: Fürstner, A.; Koglbauer, U.; Weidmann, H. *J. Carbohydr. Chem.* **1990**, *9*, 561−570. Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213−2217.

(14) This sensitivity of dealkoxyhalogenation reactions to steric effects has also been observed in the reaction of metal−graphite reagents with furanose systems.[6b]

(15) Probably in this case a 1,5-hydrogen migration from the benzyl group at O-4 to C-6 is competing favorably with the reduction of the intermediate primary radical at C-6 by SmI_2. Similar 1,5-hydrogen migrations in radical intermediates from benzylated sugar derivatives have been reported before: (a) Liotta, L. J.; Bernotas, R. C.; Wilson, D. B.; Ganem B. *J. Am. Chem. Soc.* **1989**, *111*, 783−785. (b) Martin, O. R.; Xie, F.; Kakarla, R.; Benhamza, R. *Synlett* **1993**, 165−167. (c) Barbaud, C.; Bols, M.; Lundt, I.; Sierks, M. R. *Tetrahedron* **1995**, *51*, 9063−9078 (see also ref 6b).

(16) A similar trans-directing effect of adjacent alkoxy groups has been observed in intramolecular pinacol coupling reactions promoted by samarium diiodide, and it was attributed to steric and/or electrostatic interactions involving the ketyl radical anion and the alkoxy substituent: Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125−1128.

(17) Compound **27** has the same stereochemistry as **12**. Thus, the latter could be transformed into **27** by desilylation (TBAF in THF) followed by in situ acetylation (Ac_2O, pyridine).

(18) Deuterium incorporation was almost complete (>90%) for the cyclopentane products but only 70% for the dehalogenated product **11**, as determined by ^1H NMR. This result suggests that formation of **11** is taking place via both one-electron (by hydrogen atom abstraction, probably from solvent) and two-electron (by protonation of an organosamarium intermediate) processes. See, however, ref 3a.

(19) This change in diastereoselectivity could also be due to formation of a different samarium complex in the presence of water. Water has been shown to enhance the reducing ability of SmI_2. Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008−5010. Likewise, it has been reported recently that simple alcohols also bind strongly to SmI_2 and that this binding affects the chemoselectivity of reductions of olefins by this reagent. Yacovan, A.; Hoz, S.; Bilkis, I. *J. Am. Chem. Soc.* **1996**, *118*, 261−262.

(20) Protonation of the oxygen of the ketyl radical anion by water is unlikely: α-hydroxyalkyl radicals are strong acids with $pK_a = 10.7-12.1$. Neta, P. *Adv. Phys. Org. Chem.* **1976**, *12*, 223−297. Molander has not observed any effect of proton sources on the diastereoselectivity of ketyl-olefin radical cyclizations in simple systems. Molander, G. A.; McKie *J. Org. Chem.* **1992**, *57*, 3132−3139.

(21) When this paper was in preparation, a report appeared in the literature describing the cyclization of carbohydrate-derived hex-5-enals promoted by SmI_2: Cronjé, J. J.; Holzapfel, C. W.; Williams, D. B. G. *Tetrahedron Lett.* **1996**, *37*, 1305.